sublimation rate that is also supported by the equipment (not in the choked flow region) leading to shortest drying times. A slightly more conservative set of conditions would typically be chosen to operate closer to the center of the design space.

The total heat transfer coefficient K_v of a vial is influenced by three heat transfer mechanisms: (1) radiation heat transfer (K_r) from the chamber walls and shelves above and below of a vial, (2) heat transfer due to gas conduction (K_g) between the top of the shelf and the bottom of the vials, and (3) heat transfer due to the contact between the glass vial and the shelf surface (K_c). Due to the differences in vial locations, vial manufacturing processes which lead to nonuniform vial contours, shelf inter distances, hot and cold spots on the shelf surfaces and shelf surface nonuniformity, the contribution of these three modes of heat transfer to the total K_v varies in a batch undergoing freeze-drying. Moreover, due to differences in ice nucleation temperature of different vials during freezing, $\dot{Q}$ per vial varies in a batch. Due to these batch variations in K_v and $\hat{R}_p$ different vials in a batch have different drying times. This variation in K_v and $\hat{R}_p$ should be considered when using the steady-state heat and mass transfer equations to generate the design space. Using the average values K_v and $\hat{R}_p$ for a batch of vials may lead to a situations where if the cycle is designed to run close to the boundary of the design space, there may be product failure in a subset of vials due to some of vials experiencing higher than average heat transfer (high K_v) leading to collapse or drying too slowly (high $\hat{R}_p$ and low K_v) leading to melt back and high residual moisture.

To check the validity of the mathematical model and design space, robustness studies should be carried out. At least three runs should be conducted at a set of conditions (shelf temperature, chamber pressure, time) that test the high, medium, and low limits of product temperature, primary drying time, and residual moisture. The samples from these studies should be characterized for stability (accelerated and long term). During the transfer of a cycle to a large-scale clinical or commercial dryer, modifications have to be made in the design space to account for the differences in equipment capability (choked flow or condenser overload regime), K_v, and $\hat{R}_p$. Differences in equipment capability are due to differences in equipment design and scale. Differences in K_v arise primarily due to changes in the percentage of vials on the edge of the array (edge vials) which changes the contribution of K_r to the total K_v of all the vials. Due to differences in the number of particulates in the air between a laboratory and class 100 environment, the ice nucleation temperatures and hence $\hat{R}_p$ may also differ b etween a laboratory scale and commercial scale lyophilizer. Typically, compared to a laboratory scale dryer with a plexiglass door, the value of K_v is lower in a commercial scale dryer with a stainless steel door due to reduced K_r and a reduction in the percentage of edge vials in a commercial scale dryer. The average value of $\hat{R}_p$ is expected to be higher in a commercial scale dryer due to a lower ice nucleation temperature as compared to a laboratory scale dryer. The use of a PAT tool such as TDLAS in a commercial scale dryer will enable these parameters to be estimated in a time-efficient manner.